REMARKS

Claims 1-8, 12-28, and 31-52 are pending in the application. Claims 9-11, 29, and 30 are also pending, but presently stand withdrawn from consideration as being drawn to non-elected subject matter. Applicants have cancelled claims 5, 6, 17, 20-25, 29-49, 51, and 52 without prejudice to pursuing this subject matter in one or more continuing applications; and added new claims 53-62. Claims 1-4, 7, 8, 12-16, 18, 19, 26-28, 50, and 53-62 will therefore be pending upon entry of the proposed amendments.

Applicants have amended claim 1 to incorporate the limitations of claims 5, 6, and 31. Applicants have also added the clauses "wherein the lyophilized didemnin preparation comprises a didemnin compound and a water-soluble material" and "wherein reconstitution of the lyophilized didemnin preparation with the reconstitution solution of mixed solvents provides a parenterally suitable preparation." Support for these amendments can be found throughout the specification, e.g., at the second full paragraph on page 2 and the paragraph bridging pages 3 and 4.

Applicants have amended claims 4 and 27 to be consistent with claim 1 as presently amended. Claim 28 has also been amended to be consistent with claim 12.

Applicants have amended claim 7 to depend from claim 1 instead of claim 6 (now cancelled). In addition, Applicants have deleted the phrase "is ethanol and" from claim 7. This cancelled subject matter is recaptured in new claim 57. Support for this amendments can be found throughout the specification, e.g., at the first and third full paragraphs on page 4 and claim 7 as originally filed.

Applicants have amended claim 18 to depend from claim 12 instead of claim 17 (now cancelled).

Applicants have amended claim 50 to depend from claim 12 instead of claim 48 (now cancelled). As such, each occurrence of "water" in claim 50 has been replaced with "water for injection." In addition, Applicants have deleted the phrase "is ethanol and" from claim 50. This cancelled subject matter is recaptured in new claim 58. Support for this amendments can be

found throughout the specification, e.g., at the first and third full paragraphs on page 4 and claim 7 as originally filed.

Finally, Applicants have amended claims 12 and 26 to be consistent with the amendments to claim 1.

New claims 53-56 are based on claims 13, 14, 18, and 19, respectively. Support for new claims 59-62 can be found throughout the specification, e.g., at the first and third full paragraphs on page 4 and claim 7 as originally filed.

No new matter is introduced by these amendments.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 3 and 35 are rejected for allegedly being indefinite. According to the Office (Office Action, page 2):

> Claims 3 and 35 recite the limitation 'the didemnin compound' There is insufficient antecedent basis for the limitation as claimed.

The rejection of claim 35 is moot in view of its cancellation.

Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the application, Applicants have amended claim 1 to recite a "didemnin compound." In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-8, 12-28, and 31-52 are rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Crumb et al., U.S. Patent No. 6,030,943 ("Crumb") in view of Arai, et al., U.S. Patent 4,342,744 ("Arai") "and" (Office Action, page 3) Pribish et al., U.S. Patent 6,365,597 ("Pribish"). According to the Office (Office Action, pages 6-8, emphasis added):

> Although Applicants argues a person of ordinary skill in the art would not have been led to combine Crumb and Brown, Examiner has amended this non-final rejection to include other references such as Arai and Pribish to demonstrate that the above cited references of Crumb, Arai and Pribish as a whole would **create** the claimed pharmaceutical composition and/or kit for enhanced injectable delivery of the pharmaceutical composition's active ingredient to a subject. ...
>
> Although Crumb does not expressly teach within his reference that surfactant and/or alkanol are mixed with water within Crumb's reconstitution solution, Crumb does teaches that one of ordinary skill in the art would **want** to utilize surfactant and/or wetting agents within its pharmaceutical formulation and/or container (see, e.g., column 6 lines 5-11). ...
>
> Furthermore, Arai beneficially teaches that the claimed alkanol (i.e. ethanol) is an effective delivery carrier to aid in the administration of an active ingredient to a subject (see, e.g., entire document including column 7 lines 9-26, tables and claims).
>
> Moreover, Pribish beneficially teaches that ethanol is also a preferred carrier in injectable solutions (see, e.g., entire patent including column 6 lines 17-21).
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Crumb et al.'s pharmaceutical composition and/or kit to include the active ingredient of an alkanol (i.e. ethanol) as taught by Arai and Pribish within Crumb's pharmaceutical composition and/or kit because **the three combined teachings would create the claimed pharmaceutical composition and/or kit for enhanced injectable delivery of the pharmaceutical composition's active ingredients to a subject**. Furthermore, the adjustment of other conventional working conditions (e.g., the substitution of one functional equivalent alkanol for another, the ranges of each active ingredient to create solubilization of the pharmaceutical composition, the substitution of one surfactant for the other and placing the reconstitution solution within a container such as a vial), is **deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan**.

This is respectfully traversed.

[1] Brief Summary of Claimed Subject Matter

The present claims are directed to kits and pharmaceutical compositions for the parenteral administration of didemnin compounds (e.g., aplidine, which is also known as dehydrodidemnin B).

Independent claim 1 is directed to kits that include firstly a lyophilized didemnin preparation and secondly, and separately contained, a reconstitution solution of mixed solvents. The lyophilized didemnin preparation includes a didemnin and a water-soluble material. The reconstitution solution of mixed solvents includes water for injection, an alkanol, and a nonionic surfactant, in which the water for injection is present in an amount sufficient to allow solubilization of the water soluble material, and the alkanol is present in an amount sufficient to allow solubilization of the didemnin in the lyophilized didemnin preparation. Claim 1 also requires that reconstitution of the lyophilized didemnin preparation with the reconstitution solution of mixed solvents provides a parenterally suitable preparation.

Independent claim 12 is directed to reconstituted pharmaceutical compositions that include: a didemnin compound; a water soluble material; a nonionic surfactant; an alkanol; and water for injection. The water for injection is present in an amount sufficient to allow solubilization of the water soluble material, and the alkanol is present in an amount sufficient to allow solubilization of the didemnin compound.

The claimed kits and pharmaceutical compositions address some of the problems associated with prior efforts to obtain stable, soluble pharmaceutical preparations that are suitable for the parenteral (e.g., intravenous) administration of didemnins. Stable didemnin lyophilized pharmaceutical preparations can typically be achieved by the inclusion of a bulking agent as part of the preparation. A preferred bulking agent for this purpose is mannitol, which is water soluble. The didemnins (e.g., aplidine), however, tend to have only rather limited water solubility. This difference in water solubility makes the solubilization of a didemnin (e.g., aplidine) and a water soluble adjuvant(s) (e.g., mannitol) in water based vehicles difficult. Water based vehicles, such as normal saline 0.9% NaCl, are typically the liquid vehicles of choice for intravenous routes of administration.

The inventors, in addressing the aforementioned problems, have discovered lyophilized didemnin preparations, which are both stable and permit solubilization of a didemnin (e.g., aplidine) and a water soluble adjuvant(s) (e.g., mannitol) in water based vehicles that are suitable for parenteral (e.g. intravenous) administration to a cancer patient.

[2] Crumb

Crumb discloses that aplidine can be used as an L-type calcium channel enhancer (Crumb, col. 2, lines 33-34). Crumb teaches that aplidine can be administered "intravenously or by injection" using "liquids" that contain a **single** solvent, namely **water** (see Crumb at col. 6, lines 12-18). A co-solvent (e.g., an alkanol) is never mentioned in Crumb.

According to the Office (Office Action, page 7, emphasis added):

> Crumb does teaches that one of ordinary skill in the art would **want** to utilize surfactant and/or wetting agents within its pharmaceutical formulation and/or container (**see, e.g., column 6 lines 5-11**).

"Column 6 lines 5-11" of Crumb, which is cited by the Office in the passage above, is reproduced below:

> The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

There is nothing in this passage (or anywhere else in Crumb) that would have led one to "want to utilize surfactant and/or wetting agents" (Office Action, page 7). The term "surfactants" does not even appear in this passage. Rather, the above-quoted passage from Crumb merely provides a listing of optional components that could be included in a formulation. Again, to the extent that Crumb discusses vehicles for injection of aplidine, Crumb teaches only the use of single solvent (water) based vehicles for injection, particularly for injection of aplidine in lyophilized form (Crumb at col. 6, lines 14-20, emphasis added):

> The mixtures can alternatively be dissolved in liquids such as ten percent aqueous glucose solution, isotonic saline, sterile water, or the like, and administered intravenously or by injection. Such solutions can, if desired, be **lyophilized and stored in a sterile ampoule ready for reconstitution by the addition of sterile water for ready intramuscular injection**.

In short, there is nothing in Crumb that would have led one to necessarily "want" to modify Crumb's aplidine/water-based, injectable solutions.

[3] Arai

Arai has nothing to do with injectable compositions or solubilization of cytostatic agents. Rather, Arai is concerned exclusively with "hair treatment products" (see title), i.e., compositions that are applied to the hair. Arai's hair treatment products include a polyvinyl-pyrrolidinone quaternized copolymer and a phosphate mono, di, or triester (Arai at col. 1, line 49 through col. 2, line 13). These components are quite a bit different from a didemnin. Arai discloses that his hair products can further include alcohols (Arai at col. 3, line 65 through col. 4, line 2). More particularly, Arai discloses examples of hair treatment products that include ethanol and water, which are applied to "switches" of hair (see, e.g., Arai at col. 5, lines 59-62).

[4] Pribish

Pribish discloses a genus of steroid compounds that are minimally substituted with a cyclopropoxy or cyclopropylamino group. The steroidal compounds in Pribish are quite a bit different structurally from a didemin. Pribish discusses formulations at col. 6, lines 8-45. More specifically, Pribish provides at col. 6, lines 8-33:

> For parental administration, the compounds may be administered as injectable dosages of a solution or suspension of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid such as water-in-oil or without the additions of a surfactant and other pharmaceutically acceptable excipients. Illustrative of oils which can be employed in the preparations are those of petroleum, animal, vegetable or synthetic origin. For example, peanut oil, soybean oil, and mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions, ethanols and glycols, such as propylene glycol are preferred liquid carriers, particularly for injectable solutions. The parental preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of inert glass or plastic.
>
> The solutions or suspension described above may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents, antibacterial agents such as ascorbic acid or sodium bisulfite; chelating agent such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose.

[5] The Supreme Court discussed the requirements for making rejections under 35 U.S.C. 103 in *KSR Intern. Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1742 (2007, bolded, underline emphasis added).

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.
>
> When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel*, 48 C.C.P.A. 1102, 292 F.2d 955, 956-957 (1961). As is clear from cases such as Adams, **a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art**. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, **it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does**. This is so because **inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known**.

Thus, a claim is not proved obvious merely by showing that the elements of that claim can be found in the prior art. Rather, the Office must articulate some reason as to why a person of ordinary skill in the art, at the time of the invention, would have combined the elements in the manner required by the claim.

[6] The Office has argued the prior art of record, in combination, would "create" the kits and reconstituted pharmaceutical compositions of the claims (Office Action, page 8, emphasis added):

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Crumb et al.'s pharmaceutical composition and/or kit to include the active ingredient of an alkanol (i.e. ethanol) as taught by Arai and Pribish within Crumb's pharmaceutical composition and/or kit because **the three combined teachings would create the claimed pharmaceutical composition and/or kit for enhanced injectable delivery of the pharmaceutical composition's active ingredients to a subject**.

Applicant respectfully disagree.

[A] The **only** teaching in prior art of record that concerns an injectable didemin formulation is found in Crumb, which tells one to use **single** solvent, i.e., water, based vehicles for injection of aplidine, particularly for the injection of aplidine in lyophilized form. With regard to Arai, the Office states: "Arai beneficially teaches that the claimed alkanol (i.e. ethanol) is an effective delivery carrier to aid in the administration of an active ingredient to a subject" (Office Action, page). The Office, however, fails to mention that Arai is concerned exclusively with "hair treatment products" and that Arai's ethanol-containing compositions are applied to hair, e.g., "switches" of hair. The Office's characterization of Pribish is similar to its characterization of Arai. However, as mentioned above, Pribish discloses a genus of steroid compounds, which are quite a bit different structurally from a didemnin. Pribish includes lists of carriers and adjuvants that can be used for parenteral administration of the steroid compounds. The term "ethanols" happens to appear in one of these lists. However, the only two-liquid medium explicitly mentioned in Pribish is "water-in oil" (see Pribish at col. 6, line 13), which is quite different from the two solvents required by the claims (alkanol and water).

In summary, the secondary references, Arai and Pribish, are not only unrelated to Crumb (neither has anything to do with aplidine or didemnins generally), but they are also quite unrelated to one another (Arai is exclusively about hair treatment products and Pribish is concerned exclusively with a genus of steroid compounds). Arai, in this instance, is arguably

within the purview of non-analogous art because Arai is concerned exclusively with hair treatment products and has nothing to do with injectable compositions or solubilization of cytostatic agents. The Office has not provided any reason as to why the skilled artisan would have turned to Arai for guidance in making an injectable formulation of any kind, much less one containing a didemnin.

[B] While the Office may have demonstrated that some of the elements of the present claims can be found, independently, in the prior art of record --a showing that in and of itself does not prove a claim obvious (*supra*)--, the Office has not provided any reason why one would have selected and combined all of the elements required by the present claims. Even if one were to consider Arai to be analogous art, the Office still fails to provide any reason as to why Arai's unrelated hair care products, which happen to contain some ethanol, would have led one, for example, to select and add the "ethanols" of Pribish to the "sterile water" of Crumb. There is nothing in the rejection to support the proposition that the skilled person, seeking to solubilize a didemnin in a water-based (and water soluble material containing) injectable formulation, would have combined Crumb, Arai, and Pribish (the three unrelated prior art references of record) in the manner suggested by the Office to arrive at the kits and reconstituted pharmaceutical compositions of the claims. Further, the Office also provides no reason why the skilled artisan would have included a nonionic surfactant in the reconstitution solution required by claim 1 or in the pharmaceutical composition claimed in claim 12.

[C] In summary, Applicants therefore respectfully request that the rejection be reconsidered and withdrawn because the Office, at most, has only identified the elements of the present claims in three unrelated disclosures, but has not articulated any reason why the claimed kits and pharmaceutical compositions would have been obvious at the time that the present application was filed.

[7] Applicants also wish to address the following assertion of the Office (page 8, emphasis added):

> Furthermore, the adjustment of other conventional working conditions (e.g., the substitution of one functional equivalent alkanol for another, the ranges of each active ingredient to create solubilization of the pharmaceutical composition, the substitution of one surfactant for the other and placing the reconstitution solution within a container such as a vial), is **deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan**.

It is somewhat unclear from the rejection what Applicants are allegedly optimizing. If it is Crumb's injectable aplidine formulation, then the Office has greatly minimized the differences between the claimed kits and pharmaceutical compositions. Crumb tells one to use **single** solvent --water-- based vehicles for injection of aplidine, particularly for the injection of aplidine in lyophilized form. In contrast, the present claims require the presence of a didemnin, a water soluble material, water for injection, an alkanol, and a nonionic surfactanct. Accordingly, the Applicants would not be engaged in, e.g., "substitution of one functional equivalent alkanol for another" (Office Action, page 8) or "substitution of one surfactant for the other" because there are no alkanols or surfactants present in Crumb's injectable aplidine formulation to substitute.

Even if the claimed kits and pharmaceutical compositions were the result of some level of "routine optimization" (and Applicants do not concede that this is the case here), that in and of itself would not render the present claims obvious. See the last sentence of 35 U.S.C. § 103(a), which provides: "[p]atentability shall not be negatived by the manner in which the invention was made." *See also, e.g., Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348,

> Nor are we ignorant of the fact that reference to "routine testing" or "routine experimentation" is disfavored. *See, e.g., In re Yates*, 663 F.2d 1054, 1056 n. 4 (C.C.P.A.1981) ("The Solicitor ... argues that it is 'not unobvious to discover optimum or workable ranges by routine experimentation.' In many instances, this may be true. **The problem, however, with such 'rules of patentability' (and the ever-lengthening list of exceptions which they engender) is that they tend to becloud the ultimate legal issue-obviousness-and exalt the formal exercise of squeezing new factual situations into preestablished pigeonholes**. Additionally, **the emphasis upon routine experimentation is contrary to the last sentence of section 103**.") (internal

> citation omitted); *In re Saether*, 492 F.2d 849, 854 (C.C.P.A.1974) ("In his argument that 'mere routine experimentation' was involved in determining the optimized set of characteristics, the solicitor overlooks the last sentence of 35 U.S.C. § 103.... Here we are concerned with the question of whether the claimed invention would have been obvious at the time it was made to a person having ordinary skill in the art-not how it was achieved.") (internal citation omitted); *In re Fay*, 52 C.C.P.A. 1483, 347 F.2d 597, 602 (C.C.P.A.1965) ("[W]e do not agree that 'routine experimentation' negatives patentability. The last sentence of section 103 states that 'patentability shall not be negatived by the manner in which the invention was made.' **To support the board's decision that 'routine experimentation within the teachings of the art' will defeat patentability requires a primary determination of whether or not appellants' experimentation comes within the teachings of the art. Whether the subsequent experimentation is termed 'routine' or not is of no consequence**.").

While the Office may deem the presently claimed kits and pharmaceutical compositions the result of "routine optimization," it has nonetheless has failed to show that this alleged "routine optimization" is in anyway taught or suggested in the prior art of record, and the rejection should be withdrawn for this additional independent reason.

[8] The rejection of claims 7, 50, 57, and 58 should be withdrawn for at least the following additional reason. The prior art of record does not teach or suggest the kit of claim 7, which requires that the nonionic surfactant must be 10 to 25% v/v of the solution; the alkanol (ethanol in the case of claim 57) must be 10 to 25% v/v of the solution; and the water for injection must be 50 to 80% v/v of the solution. The prior art of record also does not teach or suggest the reconstituted pharmaceutical composition of claim 50, which requires that the nonionic surfactant must be 10 to 25% v/v of the nonionic surfactant/alkanol/water for injection mix; the alkanol (ethanol in the case of claim 58) must be 10 to 25% v/v of the nonionic surfactant/alkanol/water for injection mix; and the water for injection must be 50 to 80% v/v of the nonionic surfactant/alkanol/water for injection mix.

The rejection of claims 59-62 should be withdrawn for at least the following additional reason. The prior art of record does not teach or suggest the kit of claim 59, which requires that

the alkanol (ethanol in the case of claim 60) must be 10 to 25% v/v of the solution. The prior art of record also does not teach or suggest the reconstituted pharmaceutical composition of claim 61, which requires that the alkanol (ethanol in the case of claim 62) must be 10 to 25% v/v of the nonionic surfactant/alkanol/water for injection mix.

The rejection of claims 18 and 55 should be withdrawn for at least the following additional reason. The prior art of record does not teach or suggest the use of a nonionic surfactant, much less the use of Cremophor EL.

CONCLUDING FORMALITIES

Applicants submit that all claims are in condition for allowance.

The fee in the amount of $1,050.00 for the Three Month Extension of Time to and including August 7, 2008 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14620-012US1 / JC/USP278531.

Respectfully submitted,

Date: August 4, 2008

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